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SYNERGIC STRATEGIES WITH ANTIFUNGAL ACTIVITY OF SILVER NANOPARTICLES AND AMPHOTERICIN B ON *Candida albicans* AND *Candida tropicalis*

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Pathogenic fungi were classified by the World Health Organization, according to the level of urgency and severity of the infections they cause. *C. albicans* was listed as a critical priority, while *C. tropicalis* as a high priority. Faced with the need to develop new treatments, combinatorial therapy has advantages over antifungals (ATF) for clinical use. The synergy between biogenic silver nanoparticles (AgNPs) with amphotericin B (AmB) against *C. albicans* and *C. tropicalis* was studied. The Minimum Inhibitory Concentration (MIC) and Minimum Fungicidal Concentration (CFM) of AmB and AgNPs were determined in accordance with the M27-4th ed. of the Clinical and Laboratory Standards Institute. Through the checkerboard microdilution method, synergistic combinations were studied with the concentration range of 0 - 2.2×10^6 pM AmB (y-axis) and 0 - 1.04 pM AgNPs (x-axis). These results were analyzed using the Fractional Inhibitory Concentration (FIC) indices ($FIC \leq 0.5$ synergism) and two software. The combinatorial index (CI) ($CI < 0.8$ Synergism) and the CI that caused 50% growth inhibition (IC_{50}) were calculated using CompuSyn. Using Combenefit, a synergy distribution map (chromatic scale) was analyzed based on the response to the combination. The Student t test was used for statistical analysis. The MIC and CFM presented the same value (0.26 pM NPAg and 1.3×10^5 pM AmB) in *C. albicans* and (0.13 pM AgNPs and 5.4×10^5 pM AmB) in *C. tropicalis*. In the synergistic combination (0.033 pM AgNPs + 3.4×10^4 pM AmB) selected for *C. albicans* the FIC index was 0.38, achieving a 4-fold reduction in the MIC of AmB and an 8-fold reduction in the MIC of AgNPs. The IC_{50} corresponded to 0.08 MIC AgNPs and 0.23 MIC AmB. In *C. tropicalis* the FIC index was 0.39 for the synergistic combination 0.033 pM AgNPs + 6.8×10^4 pM AmB, reaching a value 8 times lower than the MIC of AmB and 4 times lower than the MIC of AgNPs. The IC_{50} was 0.08 AgNPs MIC and 0.20 AmB MIC. Combenefit analysis confirmed the synergy between AgNPs and AmB in both species for the selected combinations, these results being consistent with those

detailed above. It is worth noting that in *C. tropicalis* a more pronounced synergy was revealed in correlation with its chromatic scale, within the concentration range 2.7×10^7 to 2.2×10^8 pM for AmB and 3.25 to 13 pM for AgNPs, compared to *C. albicans*. Synergistic combinations were found that were able to reduce the MICs of each compound for both species. In *C. tropicalis* the greatest reduction was achieved for the effective concentration of AmB with respect to *C. albicans*. This suggests the use of AgNPs as an ATF agent, decreasing the concentration of AmB when combined and thus reducing its toxicity. The creation of new ATF strategies is of great clinical importance for the treatment of mycoses.

Palabras clave: synergy - silver nanoparticles - Amphotericin B - *Candida albicans* - *Candida tropicalis*